filed as claim 23, and can find support in the specification, for example, on page 6, lines 12-17; page 45, lines 15-19; and in Example 5 (pages 78-80); claims 50 to 57 are directed to the subject matter that corresponds to claim 18 as originally filed, and can find support in the specification, for example, on page 5, lines 26-30 and in Example 7 (page 82); and claims 58 to 64 are directed to the subject matter that corresponds to claim 22 as originally filed, and can find support in the specification, for example, on page 6, lines 7-11 and page 45, line 15 through page 48, line 16.

Applicants note that the residue numbering used in the new claims is based on the data contained in the sequence listing and is fully supported by the specification as filed, for example, on pages 5-9, SEQ ID NO:3 and in Figure 1. The residue numbers in the claims are obtained by locating the residues in Figure 1 according to descriptions provided on the above-referenced pages, and then locating the corresponding residues on SEQ ID NO:3 disclosed on pages 89-91. For example, the polypeptide comprising "residues +1 through 29, inclusive, of Figure 1" disclosed on page 5 lines 13-14 (also on page 9, lines 21-22) is shown in Figure 1A. The amino acid sequence is matched to the sequence 21-49 of SEQ ID NO:3. As such, polypeptides comprising residues 21 to 49 of SEQ ID NO:3 is supported by the disclosure on pages 5 and 9 in view of Figure 1 and SEQ ID NO:3.

Since the new claims refer to amino acid sequences by use of the sequence identifier, the Examiner's concern regarding 37 CFR §1.821(d) has been addressed.

The title of the invention has been amended according to the Examiner's suggestion.

The requirement under 35 U.S.C. §112, second paragraph

Claims 32-36 are rejected as being indefinite for allegedly failing to particularly point out and distinctly identify the term "VEGF-related protein (VRP)" by claiming structural characteristics associated with the protein.

Applicants submit that the term "VEGF-related protein (VRP)" as recited in the subject claims is clearly defined in the specification by, among others, precisely the structural characteristics associated therewith. For example, "human VRP" of the present invention is defined on page 9, lines 14-22 as including a polypeptide having the full length sequence of Figure 1 (SEQ ID NO:3) as well as fragments and biologically active variants thereof. Similarly, "biologically active" for the purpose of the present invention is defined as having the ability to bind to and stimulate the phosphorylation of the Flt4 receptor. Page 10, lines 5-7. Thus, the terms as appeared in the subject claims are well defined in the specification with structural characteristics and thus distinguishable from any other proteins.

While maintaining that the subject claims are indeed definite and distinctive so far as the term "VRP" is concerned, applicants have elected to cancel existing claims 32-36 and file new claims 40-64 solely for the purpose of expediting the patent application process in a manner consistent with promoting and facilitating licensing opportunities. The rejection under 35 U.S.C. §112, second paragraph has been rendered moot and should be withdrawn.

The enablement requirement under 35 U.S.C. §112, first paragraph

Claims 32-36 are rejected as allegedly containing non-enabling subject matter. The claims are rejected because, according to the Examiner, the specification does not adequately teach how to effectively treat any disease or reach any therapeutic endpoint in humans by administering VRP. Applicants respectfully traverse the rejection.

As an initial matter, applicants contend that the Examiner has not met the initial burden to establish a *prima facie* case of lack of enablement. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). While the Examiner made general comments regarding pharmaceutical protein therapies, there are no specific reasons, findings of fact, or supporting evidence as to why the subject matter as claimed is not enabled. While references supporting a *prima facie* case of lack of enablement are not always required, specific technical reasons are always required. *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971) (cited in MPEP 2164.04; emphasis added).

Claims 32-36 have been canceled and new claims added solely for the purpose set forth above. The new claims are directed to subject matters including 1) methods for stimulating the tyrosine phosphorylation of Flt4 receptor; 2) methods for promoting growth of Flt4-expressing endothelial cells; and 3) methods for modulating a dysfunctional state characterized by lack of the Flt4 receptor activation. All the claimed methods require the use of VRP or a fragment thereof. VRP is a novel Flt4 ligand sharing homology to VEGF and was successfully isolated and characterized by the present inventors. The claims are directed to subject matter that has been adequately described in the specification and thus is enabled to a person skilled in the art at the priority date.

The VEGF-related protein (VRP) of the present invention is a novel molecule with defined structural characteristics. The specification provides detailed disclosures as to the isolation and sequence analysis of VRP nucleic acid molecule and VRP protein. The nucleic acid and amino acid sequences for full length VRP are shown in Figure 1 and SEQ ID NOS: 1-3. Thus, the polypeptides recited in the claims are fully supported and enabled by the specification.

Moreover, the specification discloses at least two aspects of functional characteristics of the newly identified VRP molecule: 1) as a ligand to the Flt4 tyrosine kinase receptor; and 2) as a VEGF homologue exerting similar cell growth promoting activity. In that regard, applicants submit that the current invention is the result of the inventors' diligent efforts in searching for an active ligand of the Flt4 receptor, a known tyrosine kinase receptor that belongs to the VEGF receptor family. As described in the specification (e.g., on page 17 and in Examples 1-3), three approaches were undertaken to identify protein that would bind and stimulate the phosphorylation of the Flt4 receptor. Numerous expression and screening assays were conducted, and as the result, one candidate ligand, VRP, was found by use of cDNA cloning techniques in combination with functional assays. Specifically, VRP was shown to be co-precipitated with a Flt4/IgG fusion protein in a precipitation assay, indicating that VRP binds to the extracellular domain of Flt4 (Example 4); and VRP's binding to Flt4 on the surface of a Flt4 expressing cell in turn activated the tyrosine phosphorylation of Flt4, as shown in a tyrosine phosphorylation assay (Example 5). Thus, the specification adequately describes the VRP as a Flt4 ligand and its use for stimulating the tyrosine phosphorylation of Flt4 in a Flt4-expressing cell.

VRP is also described in the specification as an VEGF homolog, both in terms of sequence structure and in terms of function. At the time the priority application of the present invention was filed (September 8, 1995), VEGF had been known in the art as a potent angiogenic factor that acts via endothelial cell specific tyrosine kinase receptors. VEGF's role in many biological and pathological processes had been implicated. As disclosed in the present application, VRP not only binds to a member of the VEGF receptor family, it also shares significant sequence homology with VEGF molecule. Figure 3B, for example, provides an alignment of the protein sequence of VRP with that of $VEGF_{121}$ and $PIGF_{131}$ (another VEGF-related protein) and shows the extent of the sequence homology (32% identical to $VEGF_{121}$ and 27% identical to $PIGF_{131}$; see also page 75). To further confirm that VRP exerts activities

similar to that found for VEGF, Example 7 (on page 82) was provided in which the growth of human lung endothelial cells was determined at increasing concentrations of VRP or VEGF. As shown in Figure 6, VRP promoted the growth of the tested endothelial cells, and thus shares the mitogenic activity of VEGF. Therefore, the specification provides both structural and functional evidence that VRP is a member of the VEGF protein family and is capable of exerting activities similar to that of VEGF.

The new claims 58 to 64 are directed to methods of using VRP for modulating a dysfunctional state characterized by lack of activation of the Flt4 receptor. Applicants submit that the claimed subject matter is commensurate in scope with the enabled teachings provided in the specification. As discussed above, VRP is well identified in the specification as a Flt4 ligand capable of activating its tyrosine phosphorylation. VRP is also shown to share significant homology to the well-known VEGF, both structurally and functionally. Moreover, by the time the priority application of the present invention was filed, the art had accumulated extensive knowledge regarding the VEGF and VEGF receptor families and their roles in various biological and pathological processes (see, for example, References Nos. 19, 22, 26 and 52 of the submitted IDS Form 1449). As the Examiner correctly stated, many factors are to be considered when determining whether there is sufficient evidence as a whole to support the determination of enablement. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). Applicants submit that in light of what was known in the art regarding VEGF and VEGF receptor families, one of ordinary skill would be able to practice the claimed invention by following the guidance provided in the specification, without undue experimentation.

For the reasons set forth above, Applicants submit that the enablement requirement under 35 U.S.C. §112, first paragraph has been satisfied and respectfully request the removal of the rejection.

The "written description" requirement under 35 U.S.C. §112, first paragraph

Claims 32-36 are rejected as allegedly containing subject matter which lacks written description in the specification. Applicants respectfully traverse this rejection.

According to the Examiner, claims 32-36 define a polypeptide by a function alone, i.e., it is biologically active. However, as discussed above regarding the requirement under 35 U.S.C. §112, second paragraph, the polypeptide as recited in the subject claims was clearly defined in the specification with distinctive structural characteristics as well as functional properties. For example, "human VRP" is defined on page 9, lines 14-22 as including a polypeptide having the full length sequence of Figure 1 as well as fragments and biologically active variants thereof. "Biologically active" for the purpose of the present invention is defined as having the ability to bind to and stimulate the phosphorylation of the Flt4 receptor. Page 10, lines 5-7. It is well established that claims are not to be read in a vacuum, and recitations therein are to be interpreted in light of the specification in giving them their "broadest reasonable interpretation." *In re Okuzawa*, 190 USPQ 464, 466 (CCPA 1976). See also, *In re Zletz*, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the specification; emphasis added).

Claims 32-36 have been canceled and the new claims added for the sole purpose as set forth above under the §112, 2nd paragraph rejection. The new claims are directed to polypeptides with specific structural characteristics. As such, the new claims also satisfy the written description requirement.

For the reasons set forth herein above, Applicants submit that the new claims submitted herein are now in condition for allowance. An early Notice to that effect is respectfully requested. In the event that the Examiner wishes to discuss any aspect of this response or of the application, he is invited to telephone the undersigned attorney at (650) 225-8674. Applicants will be pleased to submit documents necessary to advance this application to issuance.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extension of time and authorizes the Assistant Commissioner to

charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 07-0630. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,
GENENTECH, INC.

Date: January 31, 2001

By: 
Steven X. Cui
Reg. No. 44,637
Telephone: (650) 225-8674


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